PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:
VINEET KOHLI
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PCT

NOTIFICATION OF TRANSMITTAL OF INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

Date of Mailing *(day/month/year)*	07 MAR 2005

Applicant's or agent's file reference	IMPORTANT NOTIFICATION
PCT 21125Y	

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US03/21145	03 July 2003 (03.07.2003)	08 July 2002 (08.07.2002)

Applicant

MERCK & CO., INC.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices)(Article 39(1))(see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/US	Authorized officer
Mail Stop PCT, Attn: IPEA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450	Nashaat T. Nashed, Ph. D.
Facsimile No. (703) 305-3230	Telephone No. 571.272.1600

Form PCT/IPEA/416 (July 1992)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference PCT 21125Y	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/US03/21145	International filing date *(day/month/year)* 03 July 2003 (03.07.2003)	Priority date *(day/month/year)* 08 July 2002 (08.07.2002)
International Patent Classification (IPC) or national classification and IPC IPC(7): C12N 9/00; C07K 17/00; C12Q 1/00, 1/34; G06F 19/00 and US Cl.: 435/4, 18, 183; 530/350; 702/19		
Applicant MERCK & CO., INC.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of ___ sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of report with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand 09 February 2004 (09.02.2004)	Date of completion of this report 04 February 2005 (04.02.2005)
Name and mailing address of the IPEA/US Mail Stop PCT, Attn: IPEA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (703) 305-3230	Authorized officer Nashaat T. Nashed, Ph. D. Telephone No. 571.272.1600

Form PCT/IPEA/409 (cover sheet)(July 1998)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US03/21145

I. Basis of the report

1. With regard to the **elements** of the international application:*

☒ the international application as originally filed.

☒ the description:
pages 1-255 as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.

☒ the claims:
pages 256-270, as originally filed
pages NONE, as amended (together with any statement) under Article 19
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.

☒ the drawings:
pages 1-16, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.

☒ the sequence listing part of the description:
pages 1-2, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____ which is:

☐ the language of a translation furnished for the purposes of international search (under Rule23.1(b)).

☐ the language of publication of the international application (under Rule 48.3(b)).

☐ the language of the translation furnished for the purposes of international preliminary examination(under Rules 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

☒ contained in the international application in printed form.

☒ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages NONE

☐ the claims, Nos. NONE

☐ the drawings, sheets/~~fig~~ NONE

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

** Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).*

*** Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.*

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US03/21145

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The question whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been and will not be examined in respect of:

☐ the entire international application,

☒ claims Nos. 13-18, 29, 32, 33, 36-39, 41, 42, 46-55, and 59-74

because:

☐ the said international application, or the said claim Nos. ____ relate to the following subject matter which does not require international preliminary examination *(specify)*:

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. ____ are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. ____ are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for said claims Nos. 13-18,29,32,33,36-39,41,42,46-55 and 59-74

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. STATEMENT

Novelty (N)	Claims	Please See Continuation Sheet	YES
	Claims	Please See Continuation Sheet	NO
Inventive Step (IS)	Claims	Please See Continuation Sheet	YES
	Claims	Please See Continuation Sheet	NO
Industrial Applicability (IA)	Claims	Please See Continuation Sheet	YES
	Claims	Please See Continuation Sheet	NO

2. CITATIONS AND EXPLANATIONS
Please See Continuation Sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the questions whether the claims are fully supported by the description, are made:

Claims 1-12 are objected to as lacking clarity under PCT Rule 66.2(a)(v) because of the claims are not fully supported by the description. The description does not disclose the claimed invention in a manner sufficiently clear and complete for the claimed invention to be carried out by a person skilled.

The nature and breadth of the claimed invention encompasses any crystal comprising any kinesin spindle protein (KSP) and any ligand thereof. The description provides guidance and examples in the form of an assay to crystallize the ternary complex of the polypeptide of SEQ ID NO: 1, magnesium ADP, and variant third ligand (see examples). While human and other organisms genes encoding KSP molecular biological techniques, and genetic manipulation to make any protein and human and other organisms genes encoding KSP are known in the prior art and the skill of the artisan are well developed, knowledge regarding crystallization of proteins and their complexes is lacking. It is well established in the art that obtaining a protein or its complexes in a crystal form is highly unpredictable. The skilled artesian would be expected to screen large number of crystallization conditions, which may include screening variety of conditions in space, a micro gravity environment. A protein, which may crystallize under specific crystallization condition, its mutants or allelic variant may or may not crystallize under the same condition. In many cases, a protein that can't be crystallized, one of its specific mutants might be amenable to crystallization. Even if a crystal is obtained, it may or may not be suitable for structure determination by X-ray crystallography. Thus, searching for a crystallization conditions for a protein and its complexes that is suitable for X-ray crystallography is well outside the realm of routine experimentation and predictability in the art of success in is extremely low. The amount of experimentation to identify crystallization condition, or a mutant or fragment thereof amenable crystallization, and identify a crystal suitable structure determination X-ray crystallography is enormous. Since routine experimentation in the art does not include screening large number of crystallization conditions, mutant or fragment of KSP which can be crystallized where the expectation of obtaining the desired crystal is unpredictable, the Examiner finds that one skilled in the art would require additional guidance, such as information regarding the amino acid sequences of the KSP, mutant, or fragment thereof amenable to crystallization, and identify crystallization conditions for said KSP, mutant, or fragment thereof that produce a crystal suitable for structure determination by X-ray crystallography. Without such guidance, the experimentation left to those skilled in the art is undue.

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

V.1. Reasoned Statements:
The opinion as to Novelty was positive (Yes)with respect to claims 19-28, 30, 31, 34, 35, 40, 43-45
The opinion as to Novelty was negative (No) with respect to claims 1-12 and 56-58
The opinion as to Inventive Step was positive (Yes)with respect to claims 31
The opinion as to Inventive Step was negative(NO) with respect to claims 1-12, 19-28, 30, 34, 35, 40, 43-45, 56-58
The opinion as to Industrial Applicability was positive (YES) with respect to claims 1-12, 19-28, 30, 31, 34, 35, 40, 43-45, and 56-58
The opinion as to Industrial Applicability was negative(NO) with respect to claims NONE

Claims 56-58 lack novelty under PCT Article 33(2) as being anticipated by Blangy *et al.* (Cell 1995, Vol. 83, pp. 1159-1169).

Blangy *et al.* teach a polypeptide in Figure 1A marked HsEg5 comprising the entire polypeptide of SEQ ID NO: 1 (claim 56). Since the claim is directed to a chemical compound and the chemical compound is previously known, the identification of the conformation of the known compound would not make it patentable. The three dimensional structure of a known compound is an intrinsic property of said compound (claims 57 and 58).

Claims 1-12, and 56-58 lack novelty under PCT Article 33(2) as being anticipated by Turner *et al.* (J. Biol. Chem. 2001, Vol. 276, pp. 25496-25502).

Turner *et al.* teach the three-dimension structure of a protein named Eg5 shown in Figure 1B marked Eg5 and having identical amino acid sequence to that of SEQ ID NO: 1 of the instant application (claim 56). Since the claim is directed to a chemical compound and the chemical compound is previously known, the identification of the conformation of the known compound would not make it patentable. The three dimensional structure of a known compound is an intrinsic property of said compound (claims 57 and 58). Also, Turner *et al.* teach the crystallization of the Eg5 polypeptide as a complex with magnesium ADP, see page 25497, right column and Table 1. The crystal in monoclinic space group $P2_1$ taught by Turner *et al.* contains the same protein and first ligand as that of the instant application, but the crystal of the instant application is obtained in orthorhombic space group $P2_12_12_1$, and contains a second ligand. The structure reported by Turner *et al.* appears to be identical to that in the instant application, compare Figures 1A, and C-H of Turner *et al.* to the structure in Figure 2 of the instant application. It noted that the applicants have pointed to some differences in Figures 5 and 6, but it is not clear whether these differences can be accounted for by root mean square deviation of 2- and 0.5-angstrom units. In the absence, of other evidence the two structures are assumed to be the same (claims 1-12).

Claims 1-12, and 58 lack novelty under PCT Article 33(2) as being anticipated by Kull *et al.* (Nature 1996, Vol. 380, pp. 550-554).

Kull *et al.* teach the three-dimension structure of human kinesin motor domain corresponds to residues 1-349 of the polypeptide of SEQ ID NO: 1 of the instant application. Since the claim is directed to a chemical compound and the chemical compound is previously known, the identification of the conformation of the known compound would not make it patentable. The three dimensional structure of a known compound is an intrinsic property of said compound (claim 58). Also, Kull *et al.* teach the crystallization of the Eg5 polypeptide as a complex with magnesium ADP, see page 25497, right column and Table 1. Both the crystals taught by Kull *et al.* and by the instant application are obtained in the orthorhombic space group $P2_12_12_1$. The crystal of the instant application, however, contains a second ligand and 19 additional amino acids at the C-terminal. The structures reported by Kull *et al.* appear to be similar, if not identical, to that in the instant application, compare Figures 1b of Kull *et al.* to the structure in

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Figure 2 of the instant application. In the absence of other evidence, the two structures are assumed to be the same (claims 1-12).

Claims 19-28, 30, 34, 35, 40, and 43-45 lack an inventive step under PCT Article 33(3) as being obvious over Turner *et al.* in view of the state of the prior art as exemplified by the admitted prior art in the description on page 19, first paragraph, and the availability of various software package such as QUANTA and MODELLER, see page 34.

Turner *et al.* provide one of ordinary skill in the art with motivation to identify potential inhibitor for KSP as they teach that monastrol, known selective inhibitor for KSP, and its derivatives may be useful as an antimitotic agent, see page 25496, the paragraph bridging the two columns. Thus, it would have been obvious to one of ordinary skill in the art at the time of invention to develop a method of identifying potential inhibitors for KSP by using a computer capable of displaying representation of molecules in three dimensions. Thus, it would have been obvious to one of ordinary skill in the art to use a commercially available computer equipped with a software package such as QUANTA and MODELLER comprising the atmic coordinates defining the three dimension structure of KSP to identify compound that bind or inhbit the action of KSP by well known methods in the art. The only difference between the cited prior above and the claimed invention are the atomic coordinates. Data, which are fed into known algorithm such as QUANTA whose purpose is to compare or modify those data using series of processing steps, do not impose a change in processing steps and are thus nonfunctional descriptive material. A method used for its known purpose to compare data sets does not become nonobious merely because a new data becomes available for analysis. Nonfunctional descriptive material cannot render nonobvious an invention that has otherwise been obvious. Atomic coordinate can't render known mashine such as computer or methods for identifying inhibitors for the action of a protein patentable (19-28, 30, 34, 35, 40, and 43-45). It would have been further obvious to the ordinary skilled artisan to synthesize the potential inhibitor and contacting it with KSP.

Claims 1-12, 19-28, 30, 34-35, 40, 43-45, 56-58 meet the criteria set out in PCT Article 33(4), and thus have industrial applicability because the subject matter claimed can be made or used in industry.